CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

PROPETAMPHOS

SB # 950-325, Tolerance # 50228, Chemical Code #: 2122

August 7, 1987
Revised 3/7/88, 11/16/88, 11/5/90, 10/31/95, 1/14/99

I. DATA GAP STATUS

Combined, rat:	No data gap, no adverse effect
Chronic, dog:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, possible adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	No data gap, no adverse effect

Toxicology one-liners are attached.

** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T990114
Revised by H. Green & M. Silva, 11/5/90; M. Silva, 10/31/95 & 1/14/99.
Rectified with Pest Management Library listing through record # 098297 & volume # 062

COMBINED RAT

** 017 to -022 901986-901991. "Propetamphos, 2-Year Chronic Feeding Study in Rats". [Sandoz ID No. I 5214/81]. Sandoz LTD, Agro Development, Basle, Switzerland. 6/22/81. Combined-835-rat, propetamphos (technical grade) 91.8%, batch 4552 in the diet for 104 weeks at 0, 6, 12, and 120 ppm for 91 weeks (males) or 109 weeks (females); 55/sex/group; decrease in weight gain and CHE in 120 ppm groups; NOEL = 6 ppm (ChE inhibition of plasma and RBCs. At 120 ppm, brain ChE also affected, and clinical signs such as alopecia and red belly marks, and apparent hyperreflexia.) Reviewed and classified "not acceptable" D.S./C. Aldous, 8/9/85; Re-reviewed considering additional data [see below] and determined to be ACCEPTABLE by H.G./C. Aldous, 7/28/87.

045 050614 contains diet analysis and rebuttal/response to CDFA review of rat combined study of vols. 017 through 022, entitled "Propetamphos 2 Year Chronic Feeding Study in Rats". Considered in 7/28/87 review.

CHRONIC DOG

Subchronic Study:

058 089358, "Dose-Range Finding (Feeding) Study with Propetamphos (SAN 52.139 I) in the Dog", (T.R. Allen, S. Corney, Th. Frei, H. Luetkemeier, O. Vogel; RCC, Research and Consulting Company Ag., RCC Umweltchemie Ag., RCC Project 234270, 4/19/89). SAN 52.139 I (90.8% pure) was fed in diet, with periodic dose increases as follows: Group I: 0 (day 1-39) to 100 ppm (day 40-67); Group II: 4 ppm (day 1 to 10) to 30 ppm (day 11-14) to 60 ppm (day 15-21) to 120 ppm (day 22-28) to 180 ppm (day 29-58) to 2 Beagle dogs/sex/group. A recovery group was established on day 47 (1 male from Group II; untreated feed) for the remainder of the study. NOEL = 4 ppm (There was an increase in vomiting and/or diarrhea at $\geq$ 30 ppm. Tremors were increased at 180 ppm. At 180 ppm, both sexes showed decreased body weight and food consumption at $\geq$ 60 ppm. Liver enzymes were increased and prostate and testes weights were reduced at 180 ppm.) ChE NOEL = 30 ppm (Plasma and RBC ChE were inhibited at $\geq$ 60 ppm. Brain ChE was inhibited 40-50% in treated dogs. This included the recovery dog which was inhibited at approximately 15%.) These data are supplemental. Kishiyama & Silva, 10/10/95.

Chronic Study:

** 057 096390, "52-Week Oral Toxicity (Feeding) Study with SAN 52.139 I Technical Grade in the Dog", (T.R. Allen, S. Corney, T. Janiak, H. Luetkemeier, Th. Frei, K. Biedermann, O. Vogel, C. Springall, RCC, Research and Consulting Company AG and RCC Umweltchemie AG, Switzerland;

bone marrow atrophy (male #14) and liver necrosis (males 13 & 14) at 100 ppm. Decreased number of estrus cycles occurred in females at 100 ppm.) The systemic NOEL was previously considered to be 4 ppm (Silva, 10/12/95). However it has been changed to 20 ppm, since the increased liver weight was not considered to be an adverse effect but a reversible adaptation. ChE NOEL = 4 ppm (Plasma and RBC cholinesterase were inhibited in both sexes at $\geq$ 20 ppm. Brain ChE was inhibited in males at 100 ppm.) ACCEPTABLE. No adverse effect. (Silva, 1/14/99).

058 089358. Dose Range-finding Study for study listed under CDFA record 096390, volume 057. Worksheet available. (Kishiyama, 6/18/91).

046 050618; "SAN 52.139 I: 6-Month Feeding Study in Dogs" (Sandoz LTD, Agrochemical Research, Basle, Switzerland, #Tox 21/79, dated 2/6/79). Propetamphos technical grade 91.8%, batch #4552 (p.16/77) in the diet, 4/sex/group, at 0, 6.0, 12.0, and 24 ppm/day: dosage levels were changed to 0, 2.0, 4.0, and 24.0 ppm/day after 6 weeks due to plasma and RBC cholinesterase (ChE) inhibition. "Cholinesterase inhibition NOEL" = 2 ppm: Statistically significant inhibition of cerebral cortical ChE in males at 4 and 24 ppm, and appreciable inhibition in females at 24 ppm. Plasma ChE inhibition in both sexes at 6 ppm, and RBC ChE inhibition in both sexes at 12 ppm and above. No evidence of toxicity other than ChE inhibition. NOT ACCEPTABLE: animals were not exposed to a dosage range sufficient to elicit general chronic effects. C. Aldous, 7/31/87, with second review by FM, 2/23/87.

ONCOGENICITY RAT

(See combined rat, above)

ONCOGENICITY MOUSE

** 023-029 901992-901998). "Lifetime Oral (Diet) Carcinogenicity/Toxicity in the Mouse with SAN 52-139" (WIL Research Laboratories, Inc. # WIL-79218, 3/30/82), Oncogenicity-832-mouse, propetamphos 91.8%, batch 16/77, in the diet for 21 months, 80/sex/group, at 0, 0, 1.0, and 21.0 mg/kg/day; 70/sex/group at 6.0 mg/kg/day; 10/sex/group at 0.05 mg/kg/day; [100, 50, 40, and 50 mice/sex were designated for full term histological evaluation from controls, 1, 6, and 21 mg/kg/day groups, respectively. No significant adverse health effects indicated; NOEL = 0.05 mg/kg/day (ChE inhibition, generally dose-related: less than 30% residual brain ChE activity at 21 mg/kg/day); ACCEPTABLE (as oncogenicity study) (Report originally not acceptable in review by D.S./ C. Aldous, 8/9/85: re-evaluated and found acceptable on receipt of additional information [see below] H. Green/ C. Aldous 7/27/87).

045 050613 Contains 2 individual animal necropsy sheets which were not previously submitted with the final report (023-029;901992-901998). Other clarifications were presented, to allow acceptance of

REPRODUCTION RAT

Rangefinding Study:

062 098297 "Propetamphos: One Generation Reproduction Pilot Study in Rats", (B. Eschbach, R. Aerni, J. Hopley, P. Hertl, F. Muller, Sandoz Agro Ltd., Sandoz Project No. 433 R, July 1991). Propetamphos (90.3% pure), was fed in diet to one generation of Wistar rats (7/sex/dose) at 0, 6, 30, 120, or 180 ppm. Systemic NOEL = 30 ppm (There was decreased body weight at $\geq$ 120 ppm. Liver weights were significantly decreased at $\geq$ 120 ppm. Mortality was increased at 180 ppm.) Reproductive NOEL = 30 ppm (There was a decrease in fertility index, # of live litters, # of litters and mean pup weights at $\geq$ 120 ppm.) ChE NOEL = 6 ppm - males, with no NOEL in females (Females show significant decreases in butyryl and RBC ChE inhibition at all doses and inhibition of acetyl and brain ChE at $\geq$ 30 ppm. Males show inhibition of acetyl ChE at $\geq$ 120 ppm and acetyl, RBC and brain ChE inhibition at $\geq$ 30 ppm.) (Kishiyama & Silva, 10/13/95).

Reproduction Study:

**** 061 098296** "Propetamphos: Two Generation Reproduction Study in Rats", (B. Eschbach, R. Aerni, J. Hopley, P. Hertl, F. Muller, Sandoz Agro Ltd., Sandoz Project No. 442 R, July 1991). Propetamphos (91.8% pure), was fed in diet to Wistar rats (25/sex/dose) at 0, 4, 30, or 75 ppm for two generations. Systemic NOEL = 30 ppm (Both sexes of both generations showed significantly decreased body weights. F0 and F1 females showed increased incidence in hyperreflexia and tremors.) Reproduction NOEL = 30 ppm (Fertility was decreased in F1 males at 75 ppm. Implantation sites/litter, mean live litter size (day 0) and mean pup weights (day 0) were decreased in F2 generation at 75 ppm.) Pup NOEL = 30 ppm (The number of pups surviving to day 21 post partum was significantly decreased at 75 ppm in both generations. Along with this there was an increase in pups without milk in stomach in F1 and F2 pups at 75 ppm. For the F2 generation there was a significant decrease in pups surviving 21 days lactation index.) ChE NOEL = 4 ppm (ChE values (RBC, acetyl & butyryl were decreased in both generations of parents and pups, primarily at $\geq$ 30 ppm. Brain ChE was decreased at $\geq$ 30 ppm in both generations and both sexes. F1 pups showed decreased brain ChE at 75 ppm.) **Possible adverse effect.** Acceptable. Kishiyama & Silva, 10/17/95.

016 901985, "Propetamphos 3-Generation Study in Rats"(Sandoz LTD, Agro Development Basle, Switzerland, # 39/81, 3/5/81), reproduction-834-rat, propetamphos technical grade 91.8% batch 4552 (P18/78) in the diet, 35/sex/group, at 0, 5, 10, and 20 ppm; 3-generation, 2 litters/generation; no adverse reproductive effect noted; UNACCEPTABLE, not upgradeable (inadequate dosage levels) (D.S./C. Aldous, 8/1/85: re-reviewed 7/28/87)

D.S./C. Aldous, 8/1/85.

TERATOGENICITY RAT

** 045 050616, "Propetamphos Teratogenicity Study in Rats" (Sandoz LTD, Agrotoxicology, Basle, Switzerland, #I.6058/84, 5/30/84), propetamphos technical grade Z89%, batch P.10/82, by gavage in 2% gelatin to groups of 28, 26, 25, and 25 mated females at 0, 1.3, 3.0, and 6.0 mg/kg/day respectively on days 6 through 15 of gestation; Maternal toxicity NOEL = 1.5 mg/kg/day (drowsiness, exophthalmos, muscle tremors) was observed at 3.0 and 6.0 mg/kg/day; Developmental NOEL > 6 mg/kg/day (no embryotoxicity or teratogenicity reported). ACCEPTABLE (H.G./C. Aldous, 7/29/87. Note: Pilot study included under this record number.

016 034774 "Teratology" spin-off of reproduction study 016:901985, "Propetamphos 3-Generation Study in Rats" (Sandoz LTD, Agro Development Basle, Switzerland, # 39/81, 3/5/81). UNACCEPTABLE (dose too low to warrant consideration; apparently no examination of soft tissues of fetuses). No adverse effects indicated. D.S./C. Aldous, 8/1/85.

TERATOGENICITY RABBIT

** 045 050617, "Embryo/Fetal Toxicity and Teratogenic Potential of Propetamphos Technical Administered Orally via Stomach Tube to New Zealand White Rabbits" (Argus Research Laboratories Project 026-002, 5/25/84). Propetamphos technical, 90.9%, lot # 5RM 32832. Treatment by gavage in 0.5% carboxymethyl cellulose to 20 artificially inseminated females/group at 0 1.0, 4.0, and 8.0 mg/kg/day on days 6 through 18 of gestation; Maternal NOEL = 4.0 mg/kg/day (excess salivation and soft or liquid feces); Developmental NOEL > 8.0 mg/kg/day: no embryotoxicity or teratogenic effects observed. ACCEPTABLE H.G./C. Aldous, 7/31/87.

002 901982 "Teratology study in rabbits". IRDC, 2/27/76. Dutch Belted rabbits dosed with 0, 1, 5, or 10 mg/kg/day of VEL-4283 (94%, batch 3896; Propetamphos). Dosing was by gavage in 0.5% methocel. Thalidomide as positive control group, 150 mg/kg/day. Higher dosages were quite toxic: deaths of controls, 1, 5, and 10 mg/kg/day groups were 4/26, 8/30, 13/33, and 23/31; respectively. Treatment related signs in 5 and 10 mg/kg/day dams included: respiratory congestion, ataxia, and salivation. Apparent maternal toxicity NOEL = 1 mg/kg/day. High incidence of congested tracheal mucosa, congested lungs (possibly indicative of mechanical injury, or, as indicated by investigators, possibly compound enhancement of respiratory disease infection). No adverse effects indicated: slight evidence of delayed development at 10 mg/kg/day was noted, but determined not to be statistically significant on a per-litter basis (hypoplastic lungs, delayed ossification). These effects, if treatment related, are likely related to marked maternal toxicity. Study UNACCEPTABLE (no value in seeking to upgrade, owing to an acceptable study, above); too few surviving pregnant dams at high

GENE MUTATION

** 016 902001 "Salmonella/Mammalian - Microsome Plate Incorporation Mutagenesis Assay," (EG & Mason Research Institute, # 025-695-424-1; 5/15/80). Propetamphos technical (lot # 16/77; purity = 91.8%) was used in a plate incorporation assay in triplicate at 0 (vehicle = DMSO), 0.1, 0.3, 1.0, 3.1, and 10.0 ul/plate with Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 with and without rat liver activation and positive controls. There was a repeat trial with TA100 because of an indication of a partial loss of pkM101 with precipitation noted at 3.1 and 10 ul/plate. No gene mutation was observed. The study was previously reviewed as unacceptable (Shimer, Aldous, 8/2/85 & Gee 8/4/87) since only a single trial was run in the study (with the exception of TA100 where a second trial was because of a partial loss of pkM101). In light of the change in Federal Register (May, 1987) requirements for the Salmonella assay, where only a single trial is necessary if there are negative results, this study has been upgraded to ACCEPTABLE status. M. Silva, 11/16/88.
EPA one-liner: Acceptable. Negative for mutagenicity under activation and non activation conditions (TA-1538, TA-1537, TA-1535, TA-100, TA-98)

016 902002, "Mutagenicity Evaluation of SAN 52.139 in the Saccharomyces cerevisiae Reverse Mutation Induction Assay" (Litton Bionetics, Inc., # 20998, August, 1981), propetamphos, no purity stated, at 0, 0.5, 1.0, 10.0, 25.0, 50.0, 75.0, 100.0, and 150.0 ul/1.5 ml per well with Saccharomyces cerevisiae S138 and S211; with/without rat liver activation; incubated at 37° for 60 minutes followed by 1.0 ml spread onto 4 plates; one trial; no mutagenicity reported; UNACCEPTABLE, incomplete (insufficient information: no test article characterization, positive controls with activation were not effective in either strain but no historical control values, no evidence of cytotoxicity, single trial). (D.S. , C. Aldous, 8/1/85: Re-examined 8/4/87 by J. R. Gee and found still not acceptable. There was no new data, hence no updated worksheet).
EPA one-liner: Acceptable. Negative for mutagenicity under activation and non-activation conditions.

CHROMOSOME MUTATION

016 902003, "Micronucleus Assay on Propetamphos conducted at Litton Bionetics, Inc." (Litton Bionetics, Inc., # 3163/78, 10/16/78), propetamphos technical, 91.8%, dosed twice orally 24 hours apart, DMSO as vehicle, 4/sex/group at 0, 0.009, and 0.0009 ml/kg, dose selection stated to be based on the LD_{50} values for males and females but no evidence of toxicity reported; positive control TEM; sacrificed 6 hours after last dose; scored 1000 PCE's/animal; no induced changes reported; UNACCEPTABLE, not upgradeable (no evidence of an MTD or approach to the given values for the LD_{50} in the report, no test article lot number, single sacrifice time.) (Shimer, Aldous, 8/1/85: Data was re-examined by JRG on 8/4/87 [see paragraph which follows] without change in status of study.)
EPA one-liner: Acceptable. Negative for mutagenicity.

045 [Reference to mouse micronucleus test of 8/81 (016:902003). No record number was assigned to rebuttal comment, but comment is on last page following tab marked "Ames" in this volume]. Registrant noted that the doses used were 1/10th and 1/100th of the LD_{50}, and registrant considered this to be an appropriate treatment range. Reviewer (JRG) indicated that evidence of an MTD or toxicity to the bone marrow is necessary to demonstrate adequacy of dosage. Thus study is still NOT ACCEPTABLE. (Rebuttal response dated 8/4/87).

** 055 088212, "Study to Evaluate the Chromosome Damaging Potential of Propetamphos by its Effects on the Bone Marrow Cells of Treated Rats (According to OECD Test Guideline 475 and EPA Health Effects Test Guidelines)", (Dr. R. R. Marshall, Microtest Research Limited, University Road, Heslington, York, Y01 5DU, United Kingdom, Study # SAD 2/RBM, 2/14/90). Propetamphos (90.3% pure, lot #: 6329) was administered intraperitoneally in an in vivo cytogenetics assay to 4 or 5 Sprague-Dawley CD rats/sex/group/sampling time at 0 (corn oil) or 58 mg/kg. Bone marrow samples were taken 6, 24, and 48 hours post-dosing and 50 metaphases/animal were analyzed for chromosome aberrations. No increase in the frequency of chromosomal aberrations was observed. ACCEPTABLE. (H. Green & M. Silva, 10/29/90).

DNA DAMAGE

** 016 065637, 902004 "Evaluation of 52.139 in the Primary Rat Hepatocyte Unscheduled DNA Synthesis Assay," (Litton Bionetics, Inc. #21001; July, 1981). Propetamphos technical (Batch #: 4552; purity = 91.8%) was used on primary hepatocytes at 0 (vehicle = DMSO), 0.25, 0.5, 1.0, 2.5, 5.0, 10.0, 25.0, 50.0 and 100 nl/ml in an 18 hour exposure. 100% toxicity was observed at 100 nl/ml. The test was negative for unscheduled DNA synthesis. Originally reviewed as unacceptable (Shimer & Aldous, 8/1/85), upon receipt of the requested purity of the test material, the study has been upgraded to ACCEPTABLE**.** M. Silva, 11/14/88.
EPA one-liner: Acceptable. Negative for mutagenicity in primary rat hepatocyte unscheduled DNA synthesis assay.

NEUROTOXICITY

** 044 036121, 037503 "Acute delayed neurotoxicity study in the chicken on SAN 52-139". Bio/dynamics, study No. 6182-79. 4/8/80. Test article (SAN 52-139) = technical propetamphos, purity 91.8%. White leghorn hens administered 200 mg/kg a.i. in polyethylene glycol vehicle with atropine/2-PAM protection (unprotected LD_{50} = 78 mg/kg). Repeat administration performed day 22 of study. Hens were scored for forced exercise performance and finally sacrificed and sciatic nerve and major regions of spinal cord were extensively examined microscopically. Study ACCEPTABLE, no adverse effects indicated. D.S./D. McGee, 7/25/86.